

Attorney Docket No. P67344US0
Application No.: 09/926,630

Remarks/Arguments:

Claims 17-31, presented hereby, are pending.

Claims 1-16 are canceled hereby, without prejudice or disclaimer.

Present claim 17 corresponds to original claim 1, revised to more clearly define the instant invention. Essentially, claim 1 is rewritten, as new claim 17, following the rewriting of the claim for examination purposes as set forth on page 3 of the instant Office Action.

Present claim 20 corresponds to original claim 5, amended to include a limitation (process step), whereby the recited "suspension of tumor cells" is "incubated with interferon-gamma and tocopherol acetate," as recited in original claim 1. Claim 20 includes changes to claim 5 to overcome the objections set forth in the Office Action and to address the rejection of the claim under section 112, paragraph two, as explained below.

Present claims 18 and 19 correspond to original claim 3 and previously presented claim 4, respectively, revised to be dependent on present claim 17. Present claims 25-28 correspond to previously presented claim 11 and original claims 12-14, respectively, revised to be dependent on present claim 20. Present claims 29 and 31 correspond to original claims 15 and 16, respectively, revised to be dependent on present claim 17 and to address the rejection under section 101, as explained below. Present claim 30, which is dependent on present claim 29, recites the limitation found in original claim 2.

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The objections to claims 5, 7, and 9 are resolved by the instant amendment. Applicants wish to thank the examiner for kindly suggesting alternative claim language for overcoming the objections.

Claims 15 and 16 were rejected under 35 USC 101 for allegedly being non-statutory. Reconsideration of the rejection is requested in view of replacement claims 29 and 31, presented hereby.

"Use of" the claimed composition "for tumor therapy" in accordance with claim 15 is rewritten "A method of using the composition . . . for tumor therapy comprising administering the composition to a patient," in accordance with present claim 30. Similarly, "Use of" the claimed composition "for tumor vaccination" in accordance with claim 16 is rewritten "A method of using the composition . . . for tumor vaccination comprising administering the composition to a patient," in accordance with present claim 31. Since the rejected claims are replaced, hereby, by statutory "method" claims, withdrawal of the rejection under 35 USC 101 appears to be in order.

Claims 1-16 were rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Reconsideration is requested in view of the changes to the claims effected, hereby.

The allegedly indefinite terminology "use of a composition" is not recited in any of the present claim, which overcomes part (A) of the rejection. Part (B) of the rejection is overcome by rewriting the claims, essentially in the manner set forth "For purpose of examination," as set forth in the statement of rejection. Part (C) of the rejection is overcome because "autologous" is not recited in present claim 18, which replaces claim 2 and rejected claim 10 is canceled. Part (D) of

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the rejection is overcome by adding at the end of claim 5 "as the medicament," as recited in replacement claim 20.

Claims 5-10 and 13-16 were rejected under 35 USC 102(e) as allegedly anticipated by US20020146396 (Albert). Claims 5-10 and 14-16 were rejected under 35 USC 102(b) as allegedly anticipated by *J. Urol.*, 161, 777-792, 1999 (Hörtl). Reconsideration of the rejections under §102(e) and §102(b) is requested.

For anticipation under § 102 to exist, each and every claim limitation, as arranged in the claim, must be found in a single prior art reference. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 USPQ 253 (Fed. Cir. 1985). The absence from a prior art reference of a single claim limitation negates anticipation. *Kolster Speedsteel A B v. Crucible Inc.*, 230 USPQ 81 (Fed. Cir. 1986). A reference that discloses "substantially the same invention" is not an anticipation. *Jamesbury Corp.* To anticipate the claim, each claim limitation must "*identically* appear" in the reference disclosure. *Gechter v. Davidson*, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997) (*emphasis added*). To be novelty defeating, a reference must put the public in possession of the identical invention claimed. *In re Donahue*, 226 USPQ 619 (Fed. Cir. 1985).

The rejected claims are replaced by claims that limit the "suspension of tumor cells" to one that is "incubated with interferon-gamma and tocopheral acetate." As explicitly or implicitly acknowledged in the Office Action, neither Albert nor Hörtl discloses the added limitation. Accordingly, a single claim limitation being absent from each of the cited references, anticipation based on either of the cited references is negated. *Kolster Speedsteel A B, supra*.

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Claims 1-16 were rejected under 35 USC 103(a) as allegedly unpatentable based on Höltl in view of *Molecular Foundations of Oncology*, 95-134, 1991 (Schlom), based Albert in view of Schlom, and based on Albert in view of Schlom and US6045990 (Baust). Reconsideration of the rejections under §103(a) is requested.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art," *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970), "and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982). A "ground of rejection is simply inadequate on its face . . . [when] the cited references do not support each limitation of [the] claim." *In re Thrift*, 63 USPQ2d 2002, 2008 (Fed. Cir. 2002).

In an obviousness analysis, a reference can not be combined with another reference in such a way that destroys the invention on which one of the references is based. *Ex parte Hartmann*, 186 USPQ 366 (POBdApp 1974).

It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

In re Hedges, 228 USPQ 685, 687 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). It is the combined teachings of the prior art, taken

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as a whole, which must be considered in an obviousness analysis. *Ryko Manufacturing Co. v. Nu-Star, Inc.*, 21 USPQ2d 1053 (Fed. Cir. 1991).

The rejected claims and their present replacements recite, or the rejected claims are amended as replacement claims that recite, limitation of the "suspension of tumor cells" to one that is "incubated with interferon-gamma and tocopheral acetate." As acknowledged in the Office Action, neither Höltl nor Albert nor Schlom discloses the aforesaid limitation. Accordingly, since the cited references fail to support each limitation of the present claims, the §103(a) rejection based on the combined teachings of Höltl and Schlom and the §103(a) rejection based on the combined teachings of Albert and Schlom, alone, are both "inadequate." *Thrift*, 63 USPQ2d at 2008.

In connection with the rejection under §103(a) based on Albert in view of Schlom and Baust, and as detailed below, Baust provides no teaching or suggestion that cures the fatally deficient §103(a) disclosure provided by the combined teachings of Albert and Schlom.

The incubation of the "suspension of tumor cells" in the presence of interferon-gamma and tocopheral acetate effects a *pre-treatment* that is essential for obtaining the pronounced positive effects of the methods and composition of the presently claimed invention. Surprisingly and unexpectedly, the pronounced positive effects were observed in patients treated in accordance with the invention presently claimed – as described on page 3, ¶3, of the subject application.

Tumor cells are subjected to 2 incubation steps according to the present claims. In the 1st incubation, a purified tumor cell suspension is incubated with interferon-gamma and tocopherol acetate. In the 2nd incubation – a thawed lysate of the killed tumor cells is incubated with non-

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adherent dendritic blood cells in the presence of cytokines. From the incubated lysate/cytokine/cell mixture the "mature dendritic cells" composition is then harvested. It was totally unexpected that a crude tumor cell lysate – after treatment with the two co-factors and "feeding" to dendritic cells – is useful in the preparation of a highly effective medicament.

Thus, the present (and rejected) composition and the present method claims are characterized by, i.e., limited to, (i) isolation and suspension of tumor cells, (ii) *pre-treatment* of the tumor cells (in suspension) by incubation in the presence of interferon-gamma and tocopherol acetate, (iii) killing of the tumor cells, (iv) adding the lysate of the killed tumor cells (as an antigen) to immature dendritic cells, (v) incubating the resulting admixture in the presence of cytokines, and (iv) harvesting the claimed composition of "mature dendritic cells" from the incubated admixture.

Albert is directed to the preparation of mature dendritic cells in the presence of specific antigen preparations. According to Albert the antigens may be derived from necrotic tumor cells. Schlom, allegedly, would have motivated the skilled artisan to expose the suspension of tumor cells in Albert to interferon-gamma, but not to tocopheral acetate. Baust, allegedly, would have motivated the skilled artisan to expose the suspension of tumor cells in Albert to tocopheral acetate, but apparently not to interferon-gamma.

Accordingly, the statement of rejection alleges that, Albert in view of the *combined teachings* of Schlom and Baust provide the motivation to expose – and incubate – the Albert tumor cells in the presence of *both* interferon-gamma *and* tocopherol acetate. The allegation is incorrect.

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The teachings of Baust are directed to *preventing cell death* (apoptosis) induced during cell cryopreservation. Baust does so by treating organ and tissue cells with tocopherol acetate (vitamin E) before freezing (cryopreservation). On the other hand, Schlom is concerned with the production of monoclonal antibodies, which is not related to Baust's teaching the chilled preservation of cells at about 0°C to about 10°C.

Moreover, as opposed to Baust's treating cells with tocopherol acetate before freezing and, so, *preventing* cell death in the frozen state, the presently claimed invention requires *killing* the cells before or by freezing. The frozen cells must be dead in accordance with the present claims, which is the opposite of the objective of Baust's invention. In other words, using the teachings of Baust as alleged in the statement of rejection would destroy the invention on which Baust is based and, so, renders the obviousness rejection, under §103(a), improper. *Hartmann, supra*. The PTO cannot merely pick and choose from Baust what supports the rejection, to the exclusion of its other teachings necessary to fully appreciate what the reference fairly suggests to one of ordinary skill in the art, *Hedges, supra*, which amounts to "hindsight reconstruction." *Fine*, 5 USPQ2d at 1600.

Since Baust teaches treating cells with tocopherol acetate before freezing and, so, *preventing* cell death in the frozen state, whereas the presently claimed invention requires *killing* the cells before or by freezing, Baust effectively *teaches away* from the presently claimed invention because "a person of ordinary skill, upon reading the reference . . . would be led in a direction divergent from the path that was taken by the applicant[s]." *In re Gurley*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). A "reference teaches away if it leaves the impression that the product would not have the property

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sought by the applicant." 31 USPQ2d at 1132, citing *In re Caldwell*, 138 USPQ 243, 245 (CCPA 1963). The references taken in combination according to the §103(a) rejection effectively *teach away* from the present claims because the combination would produce a "seemingly inoperative device." *In re Spinnoble*, 160 USPQ 237, 244 (CCPA 1969).

A person skilled in the art in view of the cited references would not have expected a highly efficient medicament for tumor therapy could be obtained by pre-treating tumor cells with a combination of interferon-gamma and tocopherol acetate, as recited in the present claims. For this reason, alone, patentability of the present claims over the cited references is established. Where the claimed invention combines elements not combined in the prior art and results in a synergistic effect, i.e., a greater than additive result, this provides a sufficient showing of nonobviousness under §103. *In re Corkill*, 226 USPQ 1005 (Fed. Cir. 1985).

Additionally, applicants submit that, in contrast to the presently claimed invention, wherein a tumor cell lysate is obtained by freezing tumor cells, according to Höltl a lysate is obtained by applying hypotonic conditions (page 779, left column, "preparation of tumor cell lysates"). Also according to Höltl the step is included, whereby, "Lysates were cleared by centrifugation." The lysate is, therefore, cleared according to the reference by removing the membranes in order to obtain only the soluble components of the cytosol, which can be isolated as part of a clear aqueous solution. In contrast, the tumor cell lysate recited in the present claims is formed by freezing the tumor cell suspension and, then, thawing the frozen material.

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Considering that the tumor cell membranes are removed in the process of Höltl, a person skilled in the art, even assuming that he would consider the reference in view of Schlom, would have never considered the addition of interferon-gamma or tocopherol acetate, because these substances appear to affect the membranes according to these references. Schlom discloses that IFN gamma increases the expression of specific antigens on cells.

The subject of Albert, applicants submit, is basically a detailed study on the effect of the presence of lysates of necrotic and apoptotic cells on the maturation of dendritic cells. The reference discloses that the maturation of dendritic cells is triggered by multiple stimuli, including LPF, contact allergens, bacteria, viruses, cell products, and signaling molecules (page 22, [0213]), Therefore, Albert investigated the effect of necrotic or apoptotic tumor cells on dendritic cells and found that supernatant from necrotic cells, but not apoptotic cells, induced maturation of dendritic cells [0216]. Albert concludes that the uptake of necrotic tumor cells would lead to the initiation of T cell responses to antigens processed by the dendritic cells [0218]. However, this is an investigation of in vivo biochemical processes on the function of dendritic cells, whilst the reference does not disclose or suggest the invention of the present claims, wherein dendritic cells exposed to a tumor cell lysate are used as a medicament. Albert discloses (and claims) pharmaceutical compositions containing apoptotic cells. Necrotic cells are only mentioned in combination with apoptotic cells. The killed tumor cells in the present claims do not undergo apoptosis. Therefore, the skilled person in view of a combination of Albert, Schlom, and Baust would not have arrived at the subject matter presently claimed.

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***Request for Acknowledgment of
Foreign Priority Under 35 USC 119***

A claim to foreign priority under 35 USC 119 has been made (inventorship declaration of record) and the certified copy of the priority document received by the PTO (Form PCT/IB304, mailed 2 October 2001 by the International Bureau, of record).

Accordingly, request is made that the Examiner mark the next Office Action to acknowledge, both, the claim to §119 priority and receipt of the certified copy.

Request for Examiner's Initialed Form PTO 1449

On January 11, 2002, an Information Disclosure Statement, including completed form PTO 1449 and copies of the cited references, was filed in the PTO (a copy of the corresponding PTO receipt card is attached hereto). To date, the submitted PTO form 1449, initialed by the Examiner to show consideration of the references cited thereon, has not been received.

Accordingly, it is requested that the submitted form PTO 1449 – initialed by the Examiner – be returned.

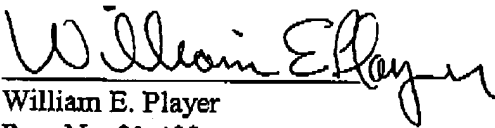
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Favorable action is requested.

Respectfully submitted,

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